REMARKS

Applicants thank Examiner Sabiha Qazi for her time and consideration during a July 17, 2007 Examiner's Interview conducted with the undersigned attorney of record John P. White. Claims 3, 4, 7, 8, 18-21, 25, 26, 31 and 33-37 are pending in the subject application. By this Amendment, applicants have amended claims 18, 31 and 33, and canceled claims 19-21, 25, and 26 without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims in the future. Support for the amendment to claims 18, 31, and 33 may be found in the specification *inter alia* at page 1, lines 15-17; and pages 21 and 22, and Table 2 at page 24. Applicants maintain that the amendments to claims 18, 31, and 33 do not raise any issue of new matter, and request entry of this Amendment. Accordingly, claims 3, 4, 7, 8, 18, 31 and 33-37 will be pending upon entry of this Amendment. Of these, claims 3, 4, 7, 8, 18 and 31 will be under examination.

Information Disclosure Statement

In the January 11, 2007 Final Office Action, the Examiner indicated that the listing of references in the specification is not a proper information disclosure statement, and that unless the references have been cited by the Examiner on form PTO-892, these references have not been considered. The Examiner further indicated that applicants must bring to the attention of the Examiner copending applications which are material to patentability of the subject application.

In response, applicants are filing with this Amendment an Information Disclosure Statement in accordance with 37 C.F.R. 1.97 and 1.98 with substitute form PTO-1449 listing all references, including related patents and copending patent applications. Applicants respectfully request that the Examiner consider the

listed references and initial and return a copy of the substitute form PTO-1449 attached hereto as **Exhibit A**.

Rejections Under 35 U.S.C. §112, First Paragraph

Written Description

The Examiner rejected claims 3, 4, 7, 8, 18-21, 25, 26, and 31 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleged that there is no written description for "treating estrogen deficiency" or "reducing bone resorption" as currently claimed. The Examiner further alleges that applicants were not in possession of the invention as now claimed.

In response, but without conceding the Examiner's ground of rejection, applicants note that claims 19-21, 25, and 26 have been canceled without disclaimer or prejudice. In addition, claim 18 has been amended to recite "A method of treating menopausal women" rather than "A method of treating estrogen deficiencies in menopausal women". Accordingly, no currently pending claim recites either "treating estrogen deficiency" or "reducing bone resorption". Applicants also maintain that, as the Examiner agreed during the July 17, 2007 Examiner's Interview, Table 2 on page 24 of the instant specification adequately describes applicants' invention as now recited in claims 18 and 31, i.e. a method of treating menopausal women with low doses of nomegestrol and a pharmaceutical composition comprising such low doses. Accordingly, applicants maintain that the specification as filed describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

Enablement

The Examiner also rejected claims 3, 4, 7, 8, 18-21, 25, 26, and 31 under 35 U.S.C. 112, first paragraph, because the specification, while acknowledged as enabling for the combination of NOMAC and estradiol valerate, allegedly does not reasonably provide enablement for treating estrogen deficiencies or reducing bone resorption.

In response, but without conceding the Examiner's ground of rejection, applicants note that claims 19-21, 25, and 26 have been canceled without disclaimer or prejudice. In addition, claim 18 has been amended to recite "A method of treating menopausal women" rather than "A method of treating estrogen deficiencies in menopausal women", so that no claim currently recites either "of these phrases.

Applicants maintain that as shown in Example 3 on pages 21-22 of the subject specification which discloses orally administering 1.5 mg of estradiol in combination with various doses of nomegestrol (5, 2.5, 1.25, or 0.625 mg) to menopausal women, several symptoms of estrogen deficiencies were assessed, i.e. genital bleeding, thickness of the endometrium, and state of the endometrium. In addition, as disclosed in Example 2 on pages 18-20, the effects of the combination therapy is assessed at the cellular level, i.e. effects of the combination of estradiol and nomegestrol acetate on endometrial cells being anti-mitotic and anti-proliferative. Accordingly, applicants maintain that amended claims 18 and 31, and claims dependent thereon, are fully enabled by applicants' specification.

In view of the preceding remarks, applicants maintain that claims 3, 4, 7, 8, 18 and 31 comply with the written description and enablement requirements of 35 U.S.C. §112, first paragraph, and request that the Examiner reconsider and withdraw these grounds of rejection.

Obviousness-Type Double Patenting Rejection

The Examiner maintained the rejection of claims 3, 4, 7, 8, 18-21, 25, 26, and 31 on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-6 of U.S. Patent No. 6,831,073.

In response, applicants respectfully traverse the Examiner's ground of rejection. Applicants note that claims 19-21, 25 and 26 have been canceled with disclaimer or prejudice.

Claim 1 of U.S. 6,831,073 provides a method for treating estrogenic deficiencies in post menopausal women comprising continuously with interruption administering to said women a composition containing from 0.5 to 3 mg of free or esterified estradiol and 1.5 to 3.75 mg of nomegestrol acetate by daily dose. Applicants note that claims 1-5 of U.S. 6,831,073 are directed to administration to post menopausal women while the present claims are directed to oral administration to menopausal women. Claim 6 of U.S. 6,831,073 recites oral administration to post menopausal women.

Claim 18 as now amended recites a method of treating menopausal women comprising continuously orally administering without interruption to menopausal women a composition containing from 0.5 to 1.5 mg of free estradiol or 1.5 to 2 mg of an estradiol ester, and from 0.625 to 1.25 mg of nomegestrol acetate per daily dose. Claim 31 as now amended recites a pharmaceutical composition in oral administrable form comprising, in combination, from 0.5 to 1.5 mg of free estradiol or 1.5 to 2 mg of an esterified estradiol and from 0.625 to 1.25 mg of nomegestrol acetate.

Applicants maintain that the present invention is based on the unexpected discovery that a lower progestative dose may be used to induce endometrium atrophy with good control of bleeding.

Applicants now claimed invention, specifically the recited 0.625 to 1.25 mg range of nomegestrol acetate per daily dose, is unobvious over claims 1-6 of U.S. Patent No. 6,831,073 because the low dose represents an unexpected result, namely the surprising decoupling of the anti-estrogenic effect of nomegestrol acetate from its progestational effect when it is administered in continuous combination with estrogens. As indicated on page 22 of the instant specification, the highest percentage of atrophic endometria was found at the lowest progestative dose. These results are expected because one skilled in the art would have expected low doses which are insufficient to induce secretory transformation of the endometrium to also be insufficient for preventing growth of the uterine mucosa to keep it in an atrophic condition.

Moreover, claims 1-6 of U.S. 6,831,073 provides methods for treating estrogenic deficiencies in post menopausal women, while applicants' claimed invention provides for methods of treating menopausal women.

In view of the remarks above, applicants maintain that amended claims 18 and 31, and claims dependent thereon are unobvious over claims 1-6 of U.S. Patent No. 6,831,073, and respectfully request that the Examiner reconsider and withdraw this nonstatutory obviousness-type double patenting ground of rejection.

Rejection Under 35 U.S.C. §103(a)

The Examiner maintained the rejection of claims 3, 4, 7, 8, 18-21, 25, 26, and 31 under 35 U.S.C. §103(a) as allegedly obvious over Plunkett et al. in view of Blanc et al. Specifically, the Examiner alleged that Plunkett et al. teach a method of hormonal treatment for menopausal disorders involving continuous administration of progestagens and estrogens. The Examiner further alleged that Blanc et al. teach continuous hormone replacement therapy combining nomegesterol acetate and gel, patch, or oral estrogen.

In response, applicants respectfully traverse the Examiner's ground of rejection. Applicants note that claims 19-21, 25 and 26 have been canceled with disclaimer or prejudice.

As stated above, amended claim 18 recites a method of treating menopausal women comprising continuously orally administering without interruption to menopausal women a composition containing from 0.5 to 1.5 mg of free estradiol or 1.5 to 2 mg of an estradiol ester, and from 0.625 to 1.25 mg of nomegestrol acetate per daily dose. Claim 31 as now amended recites a pharmaceutical composition in oral administrable form comprising, in combination, from 0.5 to 1.5 mg of free estradiol or 1.5 to 2 mg of an esterified estradiol and from 0.625 to 1.25 mg of nomegestrol acetate.

Applicants maintain that Plunkett et al. in combination with Blanc et al. do not render obvious the claimed methods or composition.

Applicants maintain that Plunkett et al. do not disclose nomegestrol acetate as a progestin candidate for use in hormonal therapy. Applicants further maintain that although Plunkett et al. specify certain ranges of dosage for certain progestins in Table IB, Plunkett et al. do not disclose which progestins are to be used or which dose is to be used with each type of progestins. In addition, of the progestatives disclosed, namely levonorgestrel, norethisterone, norethisterone acetate, norgestrel, ethynodiol diacetate, dihydrogesterone, MPA, norethylnodrel, allylestrenol, lynoestrenol, quingestanol acetate, medrogestone, norgestrienone, ethisterone and cyproterone, none are disclosed in the dosage range recited in claims 18 and 31. Specifically, none of these progestatives are administered in a dose from 0.625 to 1.25 mg.

Applicants maintain that Blanc et al. also fail to disclose the claimed dosage of applicants' invention. Blanc at al. teach nomegestrol acetate may be used in combination with estrogen at a

dose of 2.5 mg/day. As discussed above, the present invention is based on the unexpected discovery that a lower progestative dose may be used to induce endometrium atrophy with good control of bleeding. Specifically the recited low dose of 0.625 to 1.25 mg nomegestrol acetate per day is unexpected in view of Blanc et al. Applicants maintain that the decoupling of the anti-estrogenic effect of nomegestrol acetate from its progestational effect when it is administered in continuous combination with estrogens is surprising and unexpected in view of the cited prior art. One skilled in the art would not have expected such low doses of nomegestrol acetate to induce endometrium atrophy. Accordingly, applicants maintain that the combination of Plunkett et al. and Blanc et al. does not render the subject claims obvious.

In view of these remarks, applicants maintain that claims 3, 4, 7, 8, 18 and 31, as amended, define unobvious subject matter and request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §103(a).

Information Disclosure Statement

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following documents which are listed on Substitute Form PTO-1449 **(Exhibit A)** and are also listed below.

In accordance with 37 C.F.R. §1.92(a), copies of items 1-9, U.S. patents and U.S. published applications, need not be submitted. Copies of items 10-19 are attached hereto as **Exhibits 1-10**. Applicants note that items 18 and 19 (Exhibits 9 and 10) are in the French language, and thus an English language abstract has been submitted in accordance 37 C.F.R §1.98(3)(i).

1. U.S. Patent No. 5,565,443, issued October 15, 1996 (Lanquetin,

et al.);

2. U.S. Patent No. 5,843,934, issued December 1, 1998 (Simpkins);

3. U.S. Patent No. 5,888,543, issued March 30, 1999 (Gast);

4. U.S. Patent No. 5,891,867, issued April 6, 1999 (Lanquetin, et al.);

5. U.S. Patent No. 5,552,394, issued September 3, 1996 (Hodgen);

6. U.S. Patent No. 6,500,814, issued December 31, 2002 (Hesch);

7. U.S. Patent No. 6,831,073, issued December 14, 2004 (Lanquetin, et al.);

8. U.S. Patent No. 6,906,049, issued June 14, 2005 (Paris, et al.);

9. U.S. Published Application No. 2004-0220163 A1, published November 11, 2004, now abandoned;

10. U.S. Serial No. 11/649,672, filed January 3, 2007 **(Exhibit 1)**;

11. PCT International Publication No. WO 98/15279, published April 16, 1998 **(Exhibit 2)**;

12. PCT International Publication No. WO 01/30355 A1, published May 3, 2001 **(Exhibit 3)**;

13. French Patent No. 2754179 A1, issued April 10, 1998 **(Exhibit 4)**;

14. Canadian Patent No. 1332227, issued October 4, 1994 **(Exhibit**

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15. Cano, et al. (1991) "Effect of continuous oestradiol-medroxyprogesterone administration on plasma lipids and lipoproteins, Maturitas, 13(1), 35-42 **(Exhibit 6)**;

16. Catherino, William et al. (1995) "Nomegestrol Acetate, a Clinically Useful 19-Norprogesterone Derivative which Lacks Estrogenic Activity," J. Steroid Biochem. Mol. Biol., 55(2): 239-46 **(Exhibit 7)**;

17. Fraser, et al. (1989) "The effects of the addition of nomegestrol acetate to post-menopausal oestrogen therapy" Maturitas, 11(1): 21-34 **(Exhibit 8)**;

18. Jamin (1992) "Female contraception by a normal dose progestogen after 40 years of age. Possible association of nomegestrol-17-beta-estradiol acetate by percutaneous route," Rev. Fr. Gynecol. Obstet, 87(6): 370-376, English Abstract **(Exhibit 9)**; and

19. Sitruk-Ware, R., "Pharmacology of Oral Contraceptives" Rev. Prat., December 1, 1995, 45(19): 2401-2406, English Abstract **(Exhibit 10)**.

Applicants request that the Examiner review the references and make them of record in the subject application.

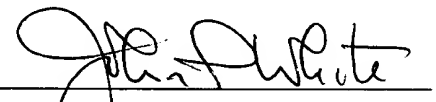
Conclusion

For the reasons set forth above, applicants maintain that the grounds for the Examiner's rejections have been overcome and respectfully request that the Examiner reconsider and withdraw these grounds of rejections and allow the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $790.00 fee for filing a Request for Continued Examination, is deemed necessary in connection with the filing of this Amendment. If any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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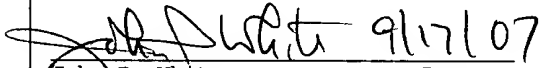

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